New backing layer for transdermal drug delivery systems: coatings based on fatty acid and beeswax on chitosan films

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Fatty acids and beeswax are known to improve barrier properties of biodegradable materials. Thanks to their hydrophobic character, they can act as a barrier against water giving to the material more occlusive properties. This work was aimed at preparing fatty acid and beeswax coatings for a transdermal drug delivery system. In order to study occlusive properties of these coatings, water vapor permeability and contact angle measurements were carried out. The most homogeneous coatings were obtained from the beeswax mixture. Coatings made from emulsified beeswax exhibit high hydrophobic properties and relatively good mechanical properties compared to chitosan film without coatings.

Keywords: fatty acid and beeswax coatings; chitosan film; water vapor permeability; transdermal drug delivery system

1. Introduction

Many different methods are used for drug administration, such as oral and intravenous ways. These routes present some disadvantages. For example, oral applications may have some gastrointestinal adverse effects and furthermore a significant fraction of drug may be eliminated by first-pass hepatic mechanism.[1] A most efficient route is the use of transdermal drug delivery system (TDDS). This system which consists of delivering a therapeutically effective amount of drug across a patient's skin eliminates the disadvantages of oral and intravenous ways. In general, this method is more patient compliant.[2] TDDS can be categorized in different types: reservoir and matrix systems with or without a rate-controlling membrane.[3] In all cases, backing layers are necessary for occlusion. Usually these layers are polyester film, polyethylene film, and polyolefin film. The developed transdermal system consists of a matrix system based only on natural components: a biopolymer film in contact with the skin, which will contain the drug and a natural fatty acid-based backing layer in contact with the outside environment.

Biopolymers have attracted interest as a matrixes for controlled release of innumerous active molecules and have been applied in the pharmaceutical, food, biomedical, and textile sectors.[4–6] Chitosan is a natural polysaccharide, biocompatible, abundant, and ecologically interesting. For TDDS elaboration, it will be used as a

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starting material because of its good film-forming properties, wound-healing benefits, bacteriostatic effects, and bioadhesive properties.[7–10]

In order to design a new green backing layer with occlusive properties, the use of fatty acids and derivatives have been studied. Due to their hydrophobic properties, fatty acids and derivatives can act indeed as a barrier toward water and so have good occlusive properties toward the outside environment. The idea of replacing synthetic polymers traditionally used by green environmental-friendly coatings has been developed over the past few years in many areas including food packaging [11] and biomedical applications.[12] They are generally added in formulations based on proteins or polysaccharides as edible food coatings in order to improve barrier properties to water.[13,14] Nevertheless, the use of fatty acids as hydrophobic coatings has not been well researched.[15,16] Recent works have reported the use of stearic acid as a coating on magnesium substrates for biomedical applications such as implants. Fatty acids have been also used as coating on nanoparticles in the encapsulation drug delivery field.[17,18] To the best of our knowledge, no one used fatty acid coatings for the design of TDDS; due to the very low solubility of fatty acids in water, their applicability is limited. Nevertheless, recently big progress has been made in this area, and it was shown that mixtures of fatty acids can form stable dispersions under controlled experimental conditions.[19–22] For instance, it is possible to disperse fatty acids in water using soluble organic counterions.[23]

The aim of this research is to prepare and characterize new green coatings made from fatty acids or their derivatives dispersed in chitosan film, to create new backing layer. Contact angle measurements, water vapor permeability (WVP), and scanning electronic microscopic images were used to characterize the coatings. The barrier properties found for the chitosan film with and without coatings were compared with a commercial patch.

2. Materials and methods

2.1. Chitosan films, fatty acids, and beeswax dispersions preparation

2.1.1. Preparation of chitosan films

Chitosan with low molecular weight (14,9000 g mol^{-1}, degree of acetylation = 12%), poly(ethylene glycol) 400 (PEG400), glycerol (GLY), acetic acid, sodium hydroxide (NaOH), and ethanol (EtOH 96%) were purchased from Sigma–Aldrich. Chitosan was dissolved at 3% (w/v) in 1% (v/v) acetic acid solution. The solution was mechanically stirred overnight at 900 rpm. Plasticizers (PEG 400 and GLY) were added into the mixture (20% of the total mass of polymer), which was mechanically stirred at 1000 rpm for 30 min. The mixture was sonicated for 10 min to remove all trapped bubbles and casted in Petri dishes (48 g per Petri dish 12 cm diameter), and then dried at 50 °C for 24 h to form thin films. After drying, the films were neutralized with 80% (v/v) ethanol solution containing NaOH of 2 g/L. The films were then washed with 80% v/v ethanol solution, removed from Petri dishes and then dried again between Teflon plates at room temperature for 3 days.

2.1.2. Preparation of the fatty acid dispersions

Stearic acid (Cooper, 98% purity) was weighed exactly in a tube, and ultrapure water was added so that to reach the concentration of 10 mg/mL. Next, the desired volumes

of 1 M stock solutions of ethanolamine (Cooper) and of guanidium hydrochloride (GuHCl; Sigma–Aldrich, 99% purity) prepared in ultrapure water were incorporated to reach equivalence (fatty acid/ethanolamine/GuHCl molar ratio $R = 1/1/1$). The mixture was melted at 80 °C for 15 min until all components were dispersed and then vigorously magnetic stirred. Then, all mixtures were stored at −20 °C, in order to avoid the degradation of the components. Prior to using, each sample was heated at 80 °C for 15 min and cooled at room temperature.[22]

2.1.3. Preparation of the beeswax dispersions

Beeswax was purchased from Cooper (with the following characteristics given by the supplier: white waxy solid; acid value of 20.5 ± 3.5 mg KOH/g; saponification value of 95.5 ± 8.5 mg KOH/g; melting point around 64 °C). The preparation of beeswax dispersions was made in the same way as the one previously described for the fatty acid dispersion.

Second formulation made from beeswax was tested according to the literature.[24] Beeswax solution was prepared by melting 0.5 g of beeswax in 100 ml of ethanol heated to 70 °C. The beeswax solution was emulsified with 25% of Tween 80 with respect to the wax content. Then, the whole mixture was homogenized for 2 min with Ultra-turrax homogenizer at 8000 rpm. In the rest of the paper, the first formulation is called not emulsified beeswax, while the second is called emulsified beeswax.

2.2. Commercial patch as reference

A commercial patch (Oesclim 37.5 µg, Solvay Pharma, Suresnes, France) was used as reference. It consists of an adhesive matrix with polyethylene vinyl acetate, ethylcellulose, octyldodecanol, dipropyleneglycol, and a coating with polyethylene vinylacetate.

2.3. Coatings preparation

The fatty acid and beeswax coatings were prepared by a dip-coating technique using an NIMA DC Mono 160 (NIMA Technology, Coventry, England) instrument. This technique involved immersing the substrates, in our case chitosan films, in the fatty acids and not emulsified beeswax, or dispersions at a controlled rate of withdrawal (240 mm/min) at room temperature. Three immersion times were studied: 1, 7, and 15 s. And the immersion was done once. In order to prepare the coating on one side of chitosan film, an adhesive tape was added on the other side of chitosan film to preserve it. After the deposition process, the samples were dried at room temperature during 2 h. Thus, chitosan films with coatings were obtained. For the rest of this paper, when referring to coatings, whatever the dispersions, the chitosan films with coatings are meant. The coatings were replicated in order to verify the reproducibility of the experiments. In the case of emulsified beeswax coatings, longer immersion times were also investigated: 60 and 120 s. Long immersion times were not investigated for beeswax coatings because films wrinkled and retracted in the extended contact with the beeswax mixture containing ethanolamine.

Thickness of films was measured using a hand-held micrometer. Ten thickness measurements were taken at random position on each film and the mean was calculated.

2.4. Coatings characterization

2.4.1. Tensile strength and elongation at break measurements

The mechanical properties were studied using a H5KT Tirius Olsen. Tensile strength (TS), and elongation at break, E, were determined in accordance with ASTM D-882-91 (1996). Seven sample strips (20 × 70 mm) of the films were cut from the different films and stored in a climatic chamber at 25 °C and 60% HR for a week before the measure. Force (N) and deformation were recorded with an initial distance of 50 mm between the grips clamping the films. TS was calculated by dividing the maximum load by the initial cross-sectional area of the sample and expressed in MPa. E was calculated as a ratio of the elongation at the point of sample rupture to the initial length of a sample as a percentage. The Young's modulus, calculated as ratio between the TS and elongation in the elastic deformation region of the stress–strain curve, was also expressed in MPa.

2.4.2. Contact angle measurements

To evaluate the surface hydrophobicity of film with and without coatings, contact angles were determined by a calibrated drop technique using a DGD Fast 60 goniometer (GBX Scientific Instruments, Bourg de Peage, France) coupled with software (Windrop++) to capture and analyze the images. Four microliters of an aqueous solution was deposited onto the substrate which was placed on an X–Y stage. The reported contact angle results were the average values of at least five measurements, with each at different positions on the substrate surface.

2.4.3. Scanning electronic microscopic images

In order to evaluate the coating homogeneity, films were visualized using a scanning electron microscope fitted with a field emission gun (SEM-FEG Quante 250 FI). Prior to observation, samples were attached on a support and coated with platinum.

2.4.4. Water vapor permeability

The WVP was determined according to the ASTM E96-95. The materials were firmly fixed onto the test cells containing anhydrous $CaCl_2$. The system was weighed using an analytical balance (0.0001 g accuracy) and then maintained at 25 °C and 60% relative humidity (RH). Inside the cell, anhydrous $CaCl_2$ absorbed the water vapor and maintained a partial pressure close to zero. The difference in partial vapor pressure between the inside and the outside of the cell was 1875 Pa. The water vapor permeated through the film to reach equilibrium and was controlled by the anhydrous $CaCl_2$ weight. With time, anhydrous $CaCl_2$ absorbed the water vapor leading to an increase in weight of the cell, which was measured at regular times. According to the method, the measurements were stopped when the weight gain passed 10% of the initial weight in $CaCl_2$. All tests were made in triplicate. The WVP was calculated using the following expression:

$$\mathrm{WVP}_{\mathrm{statique}} = \frac{\Delta m^* e}{A^* t^* \Delta P}.$$

where Δm is the weight difference (g); e, the thickness of the material (m); A, the material area (m^2); t, the time (s); ΔP, the difference in partial water vapor pressure; the unit for the WVP was g/m s Pa.

Moreover, the area of the film on which the WVP was measured was 15.90 cm^2; the samples had a diameter of 4.5 cm and the thicknesses of the samples were reported in the results part.

3. Results and discussion

Prepared chitosan films (CS) are transparent, slightly yellow, relatively homogenous in color, thin, flexible, and easy to handle. So, they can be easily used for coatings elaboration. As soon as the film was removed from the fatty acid and beeswax dispersions, the coatings were transparent. However, after 2 h at room temperature, the coatings turned white, as shown in Figure 1. The photographs illustrate that the fatty acid coatings were not homogeneous, exhibiting few white areas whereas the beeswax coatings were more homogeneous. Yet, some white local areas were still present. The white color of coatings (see Figure 1) is due to the recrystallization of fatty acids and beeswax at room temperature. In these cases, the mixture of fatty acids and beeswax were suspensions and by definition some particles of fatty acids and beeswax were not soluble. So, when the chitosan films were immersed into these mixtures, some particles were stuck onto the film surface, creating coatings heterogeneity in the coating. Moreover, the presence of ethanolamine, a weak base, induces reactions with the surface groups of chitosan film, making it difficult to prepare homogeneous coatings and even more difficult as the immersion time is prolonged. Coatings made from emulsified beeswax were transparent and homogeneous due to the fact that in that case beeswax was completely dispersed and stabilized in the emulsion system (Figure 1).

Three different immersion times: 1, 7, and 15 s were tested for all types of coatings and in addition, longer immersion times 60 and 120 s for emulsified beeswax coatings. Results proved that 1s was enough to create fatty acid coatings but not emulsified beeswax coatings. Besides, coatings obtained with 1s of immersion were less wrinkled and therefore easier to manipulate for mechanical, surface and barrier measurements. A wrinkled surface cannot be properly used to measure contact angles, as the surface is not perfectly planar. That is the reason why only results with immersion time of 1s are reported in Tables 1–3. For the emulsified beeswax coatings, even with an immersion time of 120 s, the coatings were not wrinkled and all measurements were possible.

The coatings were also observed at the microscopic scale. The scanning electronic microcopy images (Figure 2) shows the chitosan film without coating (CS) (Figure 2(a)). Figure 2(b) is that of fatty acid coatings (CS-FA) and shows a scaled

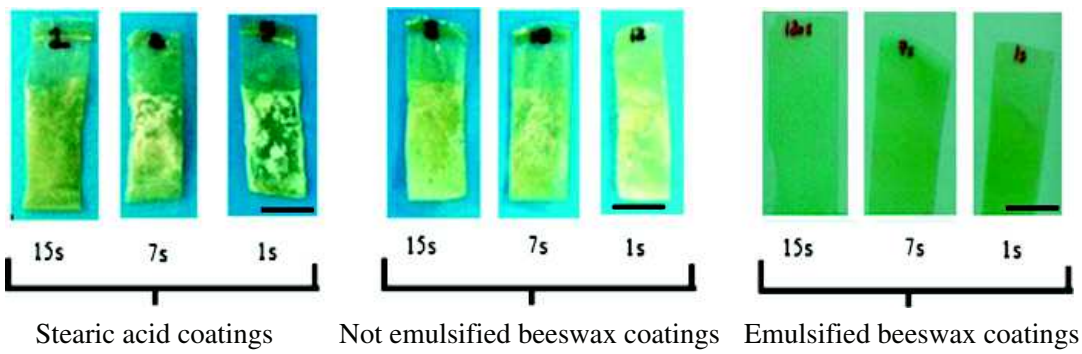

Figure 1. Photographs taken from fatty acid coatings in function of immersion time after drying for 2 h at room temperature. The scale bar represents 1.3 cm.

Table 1. Thickness of experimental films with or without coatings and commercial patch.

Sample	Description	Film thickness (μm)	Standard deviation (μm)
CS	Chitosan film without coating	129	29
CS-FA-1s	Chitosan film with fatty acid coating 1s	192	30
CS-BW-1s	Chitosan film with not emulsified beeswax coating 1s	216	24
CS-EBW-1s	Chitosan film with emulsified beeswax coating 1s	130	30
CS-EBW-120s	Chitosan film with emulsified beeswax coating 120s	131	30
Commercial Patch	Adhesive matrix: polyethylene vinyl acetate, ethylcellulose, octyldodecanol, and dipropyleneglycol Coating: polyethylene vinylacetate	316	14

surface due to a fatty acid recrystallization already observed at the macroscopic scale. Finally, Figure 2(c) and (d) illustrates the non emulsified beeswax coating (CS-BW) and the emulsified beeswax coating (CS-EBW-120s), respectively. They both exhibit surface homogeneity.

Until now in the literature, most of chitosan films with additives such as fatty acids or beeswax were generally prepared by blending all compounds, resulting in the presence of additives in the bulk.[25] In this paper, it is reported that it is possible to incorporate additives in preparation of coatings on chitosan film by dip-coating method.

As it is very important to determine the film thickness for the physical properties of films, the values are reported in Table 1. The thickness of the chitosan film without a coating was 129 ± 29 μm, whereas that of the chitosan film with fatty acid and beeswax

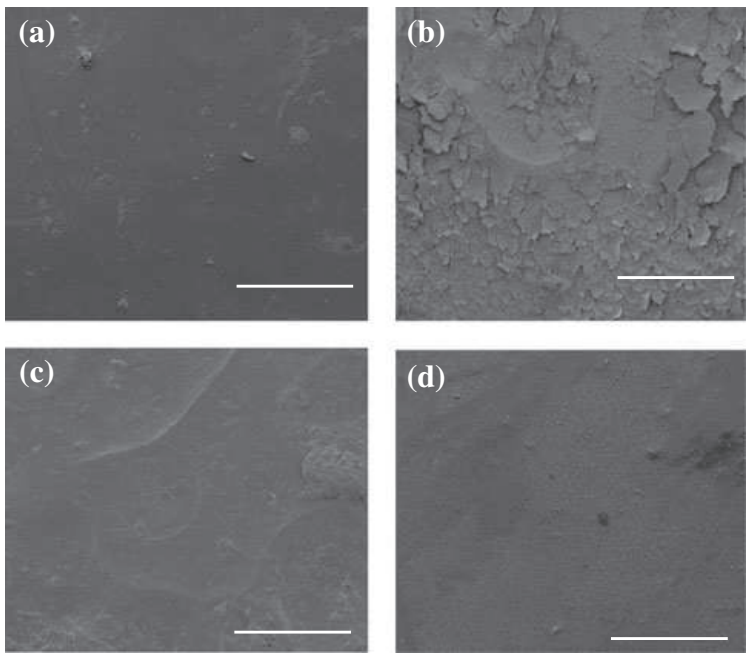

Figure 2. Scanning electron microscopic images of chitosan film without coating (a), fatty acid coating (b), beeswax coating (c), and emulsified beeswax coating (d).
Note: The scale bar represents 200 μm.

coating were thicker. The chitosan film with coating made from the emulsified beeswax exhibited a thickness similar to the chitosan film without coating. This difference should be taken into account for the results discussion. Table 1 also indicates the values of commercial patch thickness which is almost 2.5 higher than chitosan films without coating.

For the rest of the study, the focus was on the homogeneous coatings made from beeswax (emulsified or not), and not on the fatty acid coatings that were heterogeneous, in comparison with the commercial patch.

3.1. Mechanical properties

Mechanical properties are important since films for TDDS need to exhibit desirable resistance to external forces, so that damage such as tearing will not occur during use or storage. The film has to be resistant and flexible with high TS and high elongation at break values. Table 2 shows the values of TS, elongation at break (EB), and Young Modulus for chitosan film with or without coatings. As chitosan films were plasticized with Gly and PEG400, they were easy to handle. Plasticizers reduce the interaction between chitosan chains that make the chain displacement during stretching easier, which gives the film a greater ability to be deformed without breaking. The plasticizing effect is due to hydrogen bonding between O–H groups, which are present in both plasticizers and O–H and NH_2 groups of chitosan. Mechanical properties reported in the literature are lower [26] than those obtained in this study (TS 70 MPa, EB 19% and Young Modulus 2581 MPa) for chitosan films. However, the comparison of the data is very difficult for chitosan films due to the different biopolymer characteristics (molecular weight and degree of deacetylation), film preparation (different drying methods), and plasticizers contents. It appears that coatings had an influence on film mechanical properties, depending on the nature of the coatings and the dip-coating conditions. Beeswax coatings (CS-BW-1s) had significantly lower TS than chitosan films without coatings. It indicated that beeswax coatings lost resistance. This tendency has already been reported in the literature, even if most of these studies were devoted to the incorporation of fat additives into the blend and not in coatings.[23,27] The decrease of TS and EB for beeswax coatings may be explained by the heterogeneity structure of the coatings, which probably led to weakened intermolecular interactions. In the case of emulsified beeswax coatings with an immersion time of 1s (CS-EBW-1s), they had a higher value of TS than beeswax coatings (CS-BW-1s), showing an improved mechanical property compared to previous coatings (45 ± 4 and 30 ± 3 MPa, respectively). Nevertheless, their TS value is lower than chitosan film (CS) (70 ± 7 MPa). Concerning the elongation at break values, they were equivalent to those of the chitosan films. These decrease in TS and increase in EB values with the presence of hydrophobic additives have been widely discussed in

Table 2. Mechanical properties of chitosan film with or without coating and commercial patch.

Sample	TS (MPa)	EB (%)	Young modulus (Mpa)
CS	70 ± 4	19 ± 5	2581 ± 464
CS-BW-1s	30 ± 3	10 ± 2	636 ± 71
CS-EBW-1s	45 ± 4	25 ± 6	1711 ± 166
CS-EBW-120s	64 ± 15	5 ± 2	2859 ± 627
Commercial patch	95 ± 2	56 ± 2	2071 ± 115

the literature.[28] They are generally attributed to a plasticizing effect of the emulsified beeswax. The beeswax droplets emulsion could induce lubrication of chitosan and so increase the flexibility of chitosan film.

In order to improve mechanical properties of chitosan film with emulsified coatings, the immersion time was elongated until 120 s. The results show an improvement of TS value for emulsified beeswax coatings with an immersion time of 120 s (CS-EBW-120s), almost reaching the values obtained for the chitosan film: 64 ± 15 MPa for emulsified coatings against 70 ± 4 MPa for chitosan film. The values of Young Modulus were also similar to those of chitosan film, whereas the elongation at break value was lower. A long immersion time completely affected the mechanical properties of the film.

3.2. Surface and barrier properties

In order to determine the surface hydrophobicity of the coatings, contact angle measurements were carried out. In Table 3, the contact angles values are reported with the corresponding drop images. Measurements on the coatings were made just after drying for 2 h. The contact angle obtained for the chitosan film without coatings (CS) was $(79 \pm 7)°$. This value correlated well with the hydrophilic nature of chitosan and was in accordance with the literature.[29] In the case of the beeswax coating with an immersion time of 1 s (CS-BW-1s), the contact angle was $(117 \pm 7)°$, indicating much more hydrophobic surface. This increase is due to the intrinsic hydrophobic nature of beeswax and confirms that they formed monolayers on chitosan film with vertically oriented chains.[30] These results were also illustrated by the photographs of water droplets deposited on different surfaces, which significantly show the lower wettability of the surface with beeswax coatings compared with chitosan film without a coating. For emulsified beeswax coating (CS-EBW-1s and CS-EBW-120s), high contact angle value was also observed indicating a more hydrophobic surface than chitosan film. Nevertheless, the values were lower than those of the not emulsified beeswax coatings. This is probably due to the emulsion stabilization mechanisms. The beeswax emulsion was stabilized by inverse micelles (oil in water). The surface of the coatings was so covered by the polar head of micelles, inducing a lower contact angle values than in the case of not emulsified beeswax coatings. For comparison, in the case of commercial patch, the contact angle was $(88 \pm 1)°$. Surprisingly, the value

Table 3. Contact angle values and associated drop images for chitosan films and commercial patch. Measurements on the fatty acid coatings were made just after drying for 2 h.

Sample	Contact angle (°)	Drop image
CS	79 ± 7	
CS-BW-1s	117 ± 7	
CS-EBW-1s	92 ± 4	
CS-EBW-120s	98 ± 3	
Commercial patch (external face)	88 ± 1	

Table 4. WVP of chitosan film with or without coatings and commercial patch.

Sample	WVP (10^{-10} g/m s Pa)
CS	9.30 ± 0.62
CS-BW-1s	6.71 ± 0.75
CS-EBW-120s	10.12 ± 0.13
Commercial patch	0.41 ± 0.05

was not as high as was supposed, since the backing layer must have good barrier and hydrophobic properties. This result suggests that a high hydrophobic character does not lead necessary to good impermeability properties.

In order to verify this hypothesis, WVP measurements were made. The WVP of chitosan film without coatings (CS) was $(9.30 \pm 0.62) \times 10^{-10}$ g /m s Pa, whereas the one obtained for beeswax coatings (CS-BW-1s) was $(6.71 \pm 0.75) \times 10^{-10}$ g/m s Pa. The results (Table 4) showed that the not emulsified beeswax coating is 1.4 times more efficient barrier that chitosan film without coating. It is pretty well known that the presence of lipid decreased the WVP of a biopolymer film. Indeed, the crystalline structures are relatively tightly packed and tend to reduce the permeability. It appears that the imposed tortuous path of the gas molecules reduced the diffusion of gas molecules and enhanced the barrier properties of the material.[31,32] In this case, a high hydrophobic character seems to lead to an increase in barrier properties. However, it is necessary to keep in mind that the beeswax coatings were thicker than chitosan films (see Table 1). This is widely favorable to slowdown the gas diffusion and to decrease the permeability and to reinforce the barrier properties.

In the case of emulsified beeswax coatings (CS-EBW-120s), the WVP values were similar to those of chitosan films (CS). An interesting point is that our hypothesis was not confirmed in that case. The emulsified beeswax coatings indeed exhibited a higher hydrophobic character than chitosan films but have equivalent barrier properties. So, it means that hydrophobic and impermeable properties are not correlated. One good example of this result is the commercial patch. The WVP values found is around $(0.41 \pm 0.05) \times 10^{-10}$ g/m s Pa, which is characteristic for very good barrier material, whereas its hydrophobic character was little high (88°). It is also important to note that the WVP value depends on patch composition, structure, and thickness, as patch is almost two times thicker than chitosan films.

4. Conclusions

Fat addition is the most common way to improve the barrier properties of biopolymer films. Based on that idea, this paper reports the results concerning elaboration and characterization of new backing layer made from fat compounds. The preliminary experiments showed the feasibility to create new backing layer on chitosan film in preparing coatings from beeswax, emulsified or not. It was found that hydrophobic and WVP properties are not correlated. Barrier properties of coatings depend on several parameters such as thickness, structure, and also on the coatings conditions. Coatings made from emulsified beeswax exhibit high hydrophobic properties and relatively good mechanical properties compared to chitosan film without coatings. But, barrier properties are still the same as those of the chitosan films. Further investigations improved barrier and occlusive properties to reach the efficiency of commercial patch. Different ways can be used such as multilayers system which could allow filling chitosan porosity.

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